Figure 1 ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å are used.

30. (Added) The method according to claim 28, wherein in step a), the atomic coordinates of amino acids 17-392 of CnA, amino acids 1-169 of CnB, intact FKBP12 and FK506 according to Figure 1 ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å are used.

D2

REMARKS

Applicants have amended claims 19-21 for clarity. Specifically, applicants have amended claims 19-21 to recite a method "of using a computer" and to recite that said computer "comprises a machine-readable data storage medium comprising a data storage material encoded with said structure coordinates defining said binding pocket." Support for this amendment can be found throughout the specification as originally filed, e.g., at page 13, lines 5-13.

Applicants have submitted herewith an Appendix, marked up claims showing the amendments. In the Appendix, the added portions are underlined and the deleted portions are bracketed.

Applicants have added claims 25-30. Support for these claims may be found throughout the specification as originally filed, e.g., at page 18, lines 7-21.

None of these amendments adds new matter.

The Rejections

35 U.S.C. § 101

Claims 19-24 stand rejected under 35 U.S.C. § 101 as being directed to non-statutory subject matter. Regarding applicants' outputting step, the Examiner contends that outputting a quantified association to suitable hardware is "equivalent to writing down the result of a mathematical equation." The Examiner has therefore maintained the rejection set forth in the June 20, 2001 Office Action. Specifically, the Examiner contends that the independent claims recite mathematical operations "wherein the 'result' is a mere rearrangement of data," and do not produce any useful, concrete or tangible results. The Examiner further contends that the claims "do not recite any specific result, nor any actual transformation of data which would produce a result that is concrete." Applicants traverse.

To support her contentions, the Examiner cites Flook, In re Gelnovatch, In re de Castelet, and In re Abele, cases purported to involve claimed processes that do not achieve a practical application. In Flook, the Supreme Court held that a method of updating alarm limits was unpatentable because "[t]he only difference between the conventional methods of changing alarm limits and that described in respondent's applications rests in ... the mathematical algorithm." Parker v. Flook, 198 USPQ 193, 195 (1978). However, the Supreme Court later clarified that Flook "did no more than confirm the 'long-established principle' that laws of nature, natural phenomena, and abstract ideas are excluded from patent protection." AT&T, 172 F.3d at 1356 (discussing Diamond v. Diehr, 450 U.S. 175, 185 (1981)).

Similarly, in In re Gelnovatch, the CCPA held that a process for determining a set of values for use in a mathematical model of an electronic circuit was unpatentable because it "merely perform[s] a series of mathematical calculations." In re Gelnovatch, 201 USPQ 136, 145 (1979). In In re de Castelet, a method of generating a curve or family of curves was held to be drawn to nonstatutory subject matter because it recites "a process for solving a set of mathematical equations per se." In re de Castelet, 195 USPQ 439, 446 (1977). These cases simply confirm that "claims merely reciting methods of calculation" are nonstatutory. In re Gelnovatch, 201 USPQ at 143. Further, it is not clear that these cases most accurately reflect the current interpretation of what constitutes statutory subject matter under section 101 in light of State Street, discussed in more detail below.

The Examiner also cites In re Abele, wherein claims directed to producing an improved X-ray image were held to be nonstatutory because "apart from the mathematical calculations, the remaining steps were well known." In re Abele, 214 USPQ 682, 684 (1982). However, after State Street, "the Freeman-Walter-Abele test has little, if any, applicability to determining the presence of statutory subject matter." State Street Bank &Trust Co. v. Signature Financial Group, Inc., 149 F.3d 1368, 1374 (1998).

Each of Flook, In re Gelnovatch, In re de Castelet, and In re Abele was decided before the Federal Circuit reexamined the standards governing patentability of "the process of manipulation of numbers" in the landmark State Street case. See AT&T Corp v. Excel Communications, Inc., 172 F.3d 1352, 1356 (1999). More recent case law and Patent Office practice have emphasized that the requirements of section 101 are satisfied where method claims that include mathematical manipulations produce a useful, concrete, and

tangible result, rather than a mere "mathematical abstraction." See AT&T, 172 F.3d at 1359. Accordingly, claims resulting in a signal useful for billing purposes (AT&T, 172 F.3d at 1352), a share price (State Street, 149 F.3d at 1368), a smooth waveform (In re Alappat, 31 USPQ2d 1545 (1994)), or a number (Arrhythmia Research Technology Inc. v. Corazonix Corp., 22 USPQ2d 1033 (1992)) are regarded as statutory subject matter.

In particular, as noted by the court in State Street, "[t]he question of whether a claim encompasses statutory subject matter" focuses on the practical utility of the subject matter. State Street, 149 F.3d at 1375. Where the claim produces a useful, concrete, and tangible result, the claim is directed to statutory subject matter, "even if the useful result is expressed in numbers." See, id. Further, "the mere fact that a claimed invention involves inputting numbers, calculating numbers, outputting numbers, and storing numbers, in and of itself, would not render it nonstatutory subject matter." Id. at 1374. After State Street, a section 101 inquiry "focuses on whether the mathematical algorithm is applied in a practical manner to produce a useful result." AT&T, 172 F.3d at 1360. In fact, according to the MPEP, "[o]nly when the claim is devoid of any limitation to a practical application in the technological arts should it be rejected under [section 101]." MPEP § 2106 II.A.

Moreover, under this standard, there is no absolute requirement for a transformation of data step, as the Examiner contends. In particular, a physical transformation "is not an invariable requirement, but merely one example of how a mathematical algorithm may bring about a useful application." AT&T, 172 F.3d at 1358.

Applicants' claims produce a useful, concrete, and tangible result, namely, a quantified association between a chemical entity and a CnA-like or CnA/CnB-like binding

pocket. This result is not "a mere rearrangement of data," as the Examiner contends. The quantified association obtained from applicants' claimed processes is analogous to the share price obtained in State Street and to the signal useful for billing purposes in AT&T. Just as the State Street share price is useful to facilitate share trading (State Street, 149 F.3d at 1373), and the AT&T signal is useful to facilitate differential billing (AT&T, 172 F.3d at 1358), applicants' quantified association is useful to facilitate the process of drug discovery and differentiate various chemical entities based on the quantified association. Applicants' claims allow the calculation of binding affinities for calcineurin-like binding pockets. Indeed, applicants' quantified association has a "practical utility," e.g., for the design, selection, and synthesis of chemical entities, including inhibitory compounds, capable of binding to calcineurin-like binding pockets. See, e.g., specification page 18, lines 7-11. In short, applicants' result is just as useful, concrete, and tangible as the results obtained in State Street and AT&T.

Accordingly, applicants' claims are directed to statutory subject matter under section 101. Applicants therefore request that the Examiner withdraw these rejections.

35 U.S.C. § 103

Claims 19-24 stand rejected under 35 U.S.C. § 103(a) as obvious in view of United States Patent No. 5,705,335 (hereinafter "Hendry"). Specifically, the Examiner contends that Hendry teaches a "method to evaluate the ability of a chemical compound to associate with another" and "'outputting' results of [the] fitting method." The Examiner contends that the structure coordinates of applicants' claims "do not have a functional relationship with the hardware recited in the claims" and therefore "do not distinguish the

invention from the prior art." The Examiner further contends that applicants' "structure coordinates are nonfunctional descriptive matter and do not *functionally* interact with any hardware or software in the claimed methods." The Examiner therefore concludes that the claimed methods "may be performed using any set of structure coordinates." Applicants traverse.

The Examiner cites In re Gulack, 703 F.2d 1381 (1983), for the proposition that where there is no functional relationship between matter which is, by itself, non-statutory subject matter and a substrate, there is no reason to give patentable weight to the non-statutory subject matter. However, where there is a functional relationship between matter and substrate, this subject matter is given patentable weight, and the claims are patentable. Gulack, 703 F.2d at 1387. A functional relationship between matter and substrate merely requires "the existence of *differences* between the [pending] claims and the prior art." Id. at 1386 (emphasis in original). Further, "[d]ifferences between an invention and the prior art cited against it cannot be ignored merely because those differences reside in the content of the printed matter." Id. at 1385.

As amended, applicants' claims recite a method of using a computer for evaluating the ability of a chemical entity to associate with a molecule or molecular complex, wherein the computer comprises a machine-readable data storage medium comprising a data storage material encoded with structure coordinates. Both the computational means and the structure coordinates are required for the functionality of applicants' claimed methods. In particular, the computational means act on the structure

coordinates. Applicants' recited method cannot be carried out in the absence of these structure coordinates.

Accordingly, the structure coordinates are not mere nonfunctional descriptive matter to be read or outputted by a computer, as the Examiner contends. The structure coordinates are critical to applicants' process. Without these structure coordinates, applicants' process cannot be utilized for its intended function, namely, evaluating the ability of a chemical entity to associate with a CnA-like or CnA/CnB-like molecule or molecular complex. Thus, the structure coordinates of applicants' claims are functionally related to the claimed process steps. This functional relationship confers patentable weight to the structure coordinates. Accordingly, the structure coordinates distinguish applicants' claims from Hendry under Gulack.

Applicants therefore request that the Examiner withdraw these section 103 rejections.

Conclusion

Applicants request that the Examiner enter the above amendments, consider the foregoing remarks and allow the pending claims to issue. If the Examiner believes that a telephonic interview would be helpful, he is invited to call applicants' agent or attorney at any time.

Respectfully submitted,

Kristin M Joslyn

James F. Haley, Jr. (Reg. No. 27,794)
Attorney for Applicants
Larry Coury (Reg. No. 46,236)
Kristin M. Joslyn (Reg. No. 47,692)
Agents for Applicants
FISH & NEAVE
Customer No. 1473
1251 Avenue of the Americas
New York, New York 10020-1104
Tel.: (212) 596-9000
Fax: (212) 596-9090

I Hereby Certify that this Correspondence is being Deposited with the U.S. Postal Service as First Class Mail in an Envelope Addressed to: COMMISSIONER FOR PATENTS P.O. Box 2327 ARLINGTON, VA 22202 on

May 3, 2002

Lillian Garcia

Lillian Garcia

Signature of Person Signing

APPENDIX

Marked Up Claims Showing The Amendments

19. (Twice Amended) A method of using a computer for evaluating the ability of a chemical entity to associate with a crystallized molecule or molecular complex comprising a calcineurin A (CnA) binding pocket defined by structure coordinates of CnA amino acids 90, 91, 92, 118, 120, 121, 122, 150, 151, 156, 160, 199, 232, 253, 254, 256, 281, 282, 283, 284, 306, 311, 312, and 317 according to Figure 1, or a homologue of said molecule or molecular complex wherein said homologue comprises a CnA homologue binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å;

wherein said computer comprises a machine-readable data storage medium comprising a data storage material encoded with said structure coordinates defining said binding pocket and wherein said method comprises the steps of:

a. employing computational means to perform a fitting operation between the chemical entity and the CnA binding pocket or the CnA homologue binding pocket;

b. analyzing the results of said fitting operation to quantify the association between the chemical entity and the CnA binding pocket or the CnA homologue binding pocket; and

c. outputting said quantified association to a suitable output hardware.

20. (Twice Amended) A method <u>of using a computer</u> for evaluating the ability of a chemical entity to associate with a crystallized molecule or molecular complex comprising a CnA binding pocket defined by structure coordinates of CnA amino acids 90, 91, 92, 118, 120, 121, 122, 150, 151, 156, 160, 199, 281, 282, 283, 306, 311, 232, and 254, according to Figure 1, or a homologue of said molecule or molecular complex, wherein said homologue comprises a CnA homologue binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å;

<u>wherein said computer comprises a machine-readable data storage medium comprising a data storage material encoded with said structure coordinates defining said binding pocket and</u> wherein said method comprises the steps of:

a. employing computational means to perform a fitting operation between the chemical entity and the CnA binding pocket or the CnA homologue binding pocket;

b. analyzing the results of said fitting operation to quantify the association between the chemical entity and the CnA binding pocket or the CnA homologue binding pocket; and

c. outputting said quantified association to a suitable output hardware.

21. (Twice Amended) A method of using a computer for evaluating the ability of a chemical entity to associate with a crystallized molecule or molecular complex comprising a CnA/CnB binding pocket defined by structure coordinates of CnA amino acids 122, 124, 159, 160, 310, 312, 313, 314, 339, 341, 343, 344, 345, 347, 351, 352, 353, 354, 355, 356, 359, 360, and 363; and calcineurin B (CnB) amino acids 49, 50, 114, 115, 118, 119, 121, 122, 123, 124, 157, 158, 159, 161, and 162 according to Figure 1, or a homologue of said molecule or molecular complex, wherein said homologue comprises a CnA/CnB homologue binding pocket that has a root mean square deviation from the backbone atoms of said CnA and CnB amino acids of not more than 1.5 Å;

wherein said computer comprises a machine-readable data storage medium comprising a data storage material encoded with said structure coordinates defining said binding pocket and wherein said method comprises the steps of:

a. employing computational means to perform a fitting operation between the chemical entity and the CnA/CnB binding pocket or the CnA/CnB homologue binding pocket;

b. analyzing the results of said fitting operation to quantify the association between the chemical entity and the CnA/CnB binding pocket or the CnA/CnB homologue binding pocket; and

c. outputting said quantified association to a suitable output hardware.

25. (Added) A method for identifying a compound capable of associating with a molecule comprising a CnA-like binding pocket comprising the steps of:

a. using the atomic coordinates of CnA amino acids 90, 91, 92, 118, 120, 121, 122, 150, 151, 156, 160, 199, 232, 253, 254, 256, 281, 282, 283, 284, 306, 311, 312, and 317 according to Figure 1 ± a root means square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, to generate a three-dimensional structure of a molecule comprising a CnA-like binding pocket;

b. employing said three-dimensional structure to design or select said compound;

c. synthesizing said compound; and

d. contacting said compound with said molecule to determine the ability of said compound to interact with said molecule.

26. (Added) A method for identifying a compound capable of associating with a molecule comprising a CnA-like binding pocket comprising the steps of:

a. using the atomic coordinates of CnA amino acids 90, 91, 92, 118, 120, 121, 122, 150, 151, 156, 160, 199, 281, 282, 283, 306, 311, 232, and 254 according to Figure 1 ± a root means square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, to generate a three-dimensional structure of a molecule comprising a CnA-like binding pocket;

b. employing said three-dimensional structure to design or select said compound;

c. synthesizing said compound; and

d. contacting said compound with said molecule to determine the ability of said compound to interact with said molecule.

27. (Added) A method for identifying a compound capable of associating with a molecule comprising a CnA/CnB-like binding pocket comprising the steps of:

a. using the atomic coordinates of CnA amino acids 122, 124, 159, 160, 310, 312, 313, 314, 339, 341, 343, 344, 345, 347, 351, 352, 353, 354, 355, 356, 359, 360, and 363; and CnB amino acids 49, 50, 114, 115, 118, 119, 121, 122, 123, 124, 157, 158, 159, 161, and 162 according to Figure 1 ± a root means square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, to generate a three-dimensional structure of a molecule comprising a CnA/CnB-like binding pocket;

b. employing said three-dimensional structure to design or select said compound;

c. synthesizing said compound; and

d. contacting said compound with said molecule to determine the ability of said compound to interact with said molecule.

28. (Added) The method according to claim 25 or 26, wherein in step a), the atomic coordinates of a second binding pocket defined by CnA amino acids 122, 124, 159,

160, 310, 312, 313, 314, 339, 341, 343, 344, 345, 347, 351, 352, 353, 354, 355, 356, 359, 360, and 363; and CnB amino acids 49, 50, 114, 115, 118, 119, 121, 122, 123, 124, 157, 158, 159, 161, and 162 according to Figure 1 ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å are used.

29. (Added) The method according to claim 28, wherein in step a), the atomic coordinates of the entire set of structure coordinates of CnA and CnB according to Figure 1 ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å are used.

30. (Added) The method according to claim 28, wherein in step a), the atomic coordinates of amino acids 17-392 of CnA, amino acids 1-169 of CnB, intact FKBP12 and FK506 according to Figure 1 ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å are used.